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STN  Columbus  * * * * * * * * *
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=> file medline, biosis,
embase, wpids, uspatfull
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SINCE FILE      TOTAL

ENTRY    SESSION
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(ACS)

=> s (immature thymocyte!) and
caspase
L1            8 (IMMATURE
THYMOCYTE!) AND CASPASE

=> 'dup rem l1
'DUP IS NOT A RECOGNIZED
COMMAND
The previous command name
entered was not recognized by
the system.
For a list of commands
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prompt (=>).

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2            4 DUP REM L1 (4
DUPLICATES REMOVED)

=> d l2 1-4 bib ab

L2   ANSWER 1 OF 4  MEDLINE
DUPLICATE 1
AN   1998363455     MEDLINE
DN   98363455
TI   Glucocorticoid-induced
thymocyte apoptosis: protease-
dependent activation
     of cell shrinkage and DNA
degradation.
AU   Hughes F M Jr; Cidlowski
J A
CS   Laboratory of Signal
Transduction, National
Institute of Environmental
     Health Sciences, National
Institutes of Health, Research
Triangle Park, NC
     27709, USA.
SO   JOURNAL OF STEROID
BIOCHEMISTRY AND MOLECULAR
BIOLOGY, (1998 Apr) 65 (1-6)
     207-17.
     Journal code: AX4. ISSN:
0960-0760.
CY   ENGLAND: United Kingdom
DT   Journal; Article;
(JOURNAL ARTICLE)
LA   English
FS   Priority Journals; Cancer
Journals
EM   199810
EW   19981005
AB   Glucocorticoids are well
known to stimulate apoptosis
in   ***immature***
       ***thymocytes***  .
Apoptosis in this and other
cells is characterized by
     cell shrinkage, DNA
fragmentation and activation
of a class of proteases
     named caspases. We have
utilized the flow cytometer to
evaluate the
```

coordinate regulation of cell shrinkage and DNA fragmentation in glucocorticoid-treated rat thymocytes and explore the role of caspases upstream of both changes. The results indicate that the activation of apoptosis by glucocorticoids in a cell population is an asynchronous event with only a percentage of the cells displaying apoptotic characteristics at any given time. Both cell shrinkage and chromatin degradation are tightly coupled with similar proportions of the cells displaying each characteristic. The coordinate appearance of these characteristics may suggest a similar mechanism of regulation. Incubation of thymocytes with the general ***caspase*** inhibitor Z-VAD-FMK completely blocked both cell shrinkage and DNA fragmentation in spontaneous and glucocorticoid-induced thymocyte apoptosis, implicating an early upstream role for proteases in the activation of thymocyte apoptosis.

L2 ANSWER 2 OF 4 MEDLINE
AN 1998031728 MEDLINE
DN 98031728
TI CD4+ CD8+ thymocytes are preferentially induced to die following CD45 cross-linking, through a novel apoptotic pathway.
AU Lesage S; Steff A M; Philippoussis F; Page M; Trop S; Mateo V; Hugo P
CS Institut de Recherches Cliniques de Montreal, Quebec, Canada.
SO JOURNAL OF IMMUNOLOGY, (1997 Nov 15) 159 (10) 4762-71.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199801
EW 19980104
AB Ligation of the protein tyrosine phosphatase CD45 on both mature and immature T cells modulates the amplitude of TCR-mediated signals. In this work, we have evaluated the consequences of CD45 ligation on immature T cells, in the absence of TCR engagement. Cross-linking of CD45 on thymocytes by mAbs led to the induction of cellular death, characterized by a reduction in mitochondrial membrane potential (delta psi(m)), production of reactive oxygen species, loss in membrane asymmetry, exposure of phosphatidylserine residues, and incorporation of vital dyes.
In sharp contrast to most stimuli causing thymocyte death, CD45 cross-linking did not lead to DNA degradation. Cell death was not blocked by Bcl-2 overexpression or treatment with ***caspase*** inhibitor. However, death was inhibited by the addition of scavengers of reactive

oxygen species. We also established that susceptibility to CD45-mediated death is acquired during the transition of early CD4- CD8- TCR- T cell precursors into CD4+ CD8+ TCR- thymocytes and is increased with further acquisition of surface TCR on these cells. Moreover, mature thymocytes were much less sensitive to CD45 cross-linking than CD4+ CD8+ cells. We propose that during T cell development, CD45 ligation could induce the death of those ***immature*** ***thymocytes*** that do not fulfill the requirements for positive selection.

L2 ANSWER 3 OF 4 MEDLINE
AN 97211818 MEDLINE
DN 97211818
TI Apoptosis of ***immature*** ***thymocytes*** mediated by E2/CD99.
AU Bernard G; Breittmayer J P; de Matteis M; Trampont P; Hofman P; Senik A; Bernard A
CS INSERM Unit 343 Archet Hospital, Nice, France.
SO JOURNAL OF IMMUNOLOGY, (1997 Mar 15) 158 (6) 2543-50. Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199706
AB E2/CD99 is a 32-kDa transmembrane molecule that does not belong to any known family of proteins. It appears to regulate adhesion properties of T cells as previously reported, in particular, the induction of homotypic adhesion in CD4+ CD8+ thymocytes. Apoptosis induced via E2/CD99 displays characteristic morphologic features, but includes early mitochondrial alterations and phosphatidylserine exposure at the outer leaflet of the plasma membrane. It is not followed by detectable DNA fragmentation, and its time course is much longer than apoptosis induced via the Fas/CD95 pathway. It requires 18 h for completion. E2/CD99-induced apoptosis does not require any RNA or protein synthesis and still occurs following blockage of the Fas pathway. It is, however, dependent on CPP32 and IL-1beta-converting enzyme-type cysteine proteases, as shown by blockade with their respective specific inhibitors. This effect is restricted to double-positive thymocytes carrying an intermediate density of CD3 and including all CD69+ cells. Thus, E2/CD99 apears to mediate a distinctive apoptotic signal at a critical stage of thymocyte differentiation, i.e., when positive selection is known to occur.

L2 ANSWER 4 OF 4 MEDLINE DUPLICATE 2
AN 97315169 MEDLINE
DN 97315169

TI T-cell receptor ligation by peptide/MHC induces activation of a ***caspase*** in ***immature*** ***thymocytes*** : the molecular basis of negative selection.
AU Clayton L K; Ghendler Y; Mizoguchi E; Patch R J; Ocain T D; Orth K; Bhan A K; Dixit V M; Reinherz E L
CS Dana-Farber Cancer Institute, Department of Medicine, Harvard Medical School, Boston, MA 02115, USA.
NC AI19807 (NIAID) DK43551 (NIDDK) DK47677 (NIDDK) +
SO EMBO JOURNAL, (1997 May 1) 16 (9) 2282-93. Journal code: EMB. ISSN: 0261-4189.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199709
EW 19970902
AB T-cell receptors (TCRs) are created by a stochastic gene rearrangement process during thymocyte development, generating thymocytes bearing useful, as well as unwanted, specificities. Within the latter group, autoreactive thymocytes arise which are subsequently eliminated via a thymocyte-specific apoptotic mechanism, termed negative selection. The molecular basis of this deletion is unknown. Here, we show that TCR triggering by peptide/MHC ligands activates a ***caspase*** in double-positive (DP) CD4+ CD8+ thymocytes, resulting in their death. Inhibition of this enzymatic activity prevents antigen-induced death of DP thymocytes in fetal thymic organ culture (FTOC) from TCR transgenic mice as well as apoptosis induced by anti-CD3epsilon monoclonal antibody and corticosteroids in FTOC of normal C57BL/6 mice. Hence, a common ***caspase*** mediates immature thymocyte susceptibility to cell death.

=> s identif? and (enhanc? caspase)
L3 4 IDENTIF? AND (ENHANC? CASPASE)

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4 2 DUP REM L3 (2 DUPLICATES REMOVED)

=> d l4 1-2 bib ab

L4 ANSWER 1 OF 2 USPATFULL
AN 1999:4438 USPATFULL
TI SF caspase-1 and compositions for making and methods of using the same
IN Alnemri, Emad S., Ambler, PA, United States
Fernandes-Alnemri, Teresa, Ambler, PA, United States
Litwack, Gerald, Bryn Mawr, PA, United States
PA Thomas Jefferson University, Philadelphia, PA, United States (U.S. corporation)
PI US 5858778 19990112
AI US 1996-773608 19961227 (8)
DT Utility

EXNAM Primary Examiner: Wax, Robert A.; Assistant Examiner: Hobbs, Lisa J.
LREP Woodcock Washburn Kurtz Mackiewicz & Norris LLP
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 14 Drawing Figure(s); 10 Drawing Page(s)
LN.CNT 994
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A substantially pure protein, Caspase-1, is disclosed. An isolated nucleic acid molecule that comprises a nucleic acid sequence that encodes Caspase-1, is disclosed. An isolated nucleic acid molecule consisting of a nucleic acid sequence that encodes Caspase-1, or a fragment thereof having at least 10 nucleotides is disclosed. Recombinant expression vector comprising a nucleic acid sequence that encodes Caspase-1 and host cells comprising the recombinant expression vector are disclosed. Oligonucleotide molecule comprising a nucleotide sequence complimentary to a nucleic acid sequence that encodes Caspase-1 of at least 5 nucleotides are disclosed. Antibodies that binds to an epitope on Caspase-1 are disclosed. Methods of ***identifying*** modulators and substrates of Caspase-1 are disclosed.

L4 ANSWER 2 OF 2 MEDLINE DUPLICATE 1
AN 1998298186 MEDLINE
DN 98298186
TI Phosphorylation of PITSLRE p110 isoforms accompanies their processing by caspases during Fas-mediated cell death.
AU Tang D; Gururajan R; Kidd V J
CS Department of Tumor Cell Biology, St. Jude Children's Research Hospital, Memphis, Tennessee 38101, USA.
NC GM 44088 (NIGMS)
CA 21765 (NCI)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Jun 26) 273 (26) 16601-7.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199810
EW 19981002
AB A number of cellular proteins have been ***identified*** as caspase targets during cell death, including the PITSLRE protein kinases. These targets generally fall into one of three possible categories: 1) other caspases, 2) proteins that are inactivated during apoptosis, and 3) proteins that are required for execution of the cell death program. However, not all proteins are cleaved by caspases during apoptosis. Why only specific proteins are destined to be processed by caspases during cell death is currently not clear. Here we show that multiple caspase-like

activities are involved in the processing of the PITSLRE p110 isoforms
during Fas-induced apoptosis in Jurkat T-cells. Three p110 caspase
cleavage sites have been mapped to the amino-terminal domain of p110 and
verified by site-directed mutagenesis. Curiously, the mutagenesis studies
revealed that cleavage of two juxtaposed caspase sites is necessary for
the complete processing of this protein during cell death in vivo.
Finally, we demonstrate that the PITSLRE p110 protein is rapidly
phosphorylated during Fas-induced apoptosis in Jurkat cells and that
phosphorylation of an amino-terminal portion of the protein may
enhance ***caspase*** cleavage in this region.

=> s thymocyte? and (apoptosis)
L5 3734 THYMOCYTE? AND (APOPTOSIS)

=> s l5 and ("ICE" or caspase)
L6 285 L5 AND ("ICE" OR CASPASE)

=> s l6 and assay
L7 80 L6 AND ASSAY

=> s l7 and (caspase activity)
L8 3 L7 AND (CASPASE ACTIVITY)

=> d l8 1-3 bib ab

L8 ANSWER 1 OF 3 MEDLINE
AN 1999336751 MEDLINE
DN 99336751
TI Application of a fluorometric ***assay*** to detect ***caspase*** ***activity*** in thymus tissue undergoing ***apoptosis*** in vivo.
AU Gorman A M; Hirt U A; Zhivotovsky B; Orrenius S; Ceccatelli S
CS Institute of Environmental Medicine, Division of Toxicology, Karolinska
Institutet, Stockholm, Sweden.
SO JOURNAL OF IMMUNOLOGICAL METHODS, (1999 Jun 24) 226 (1-2) 43-8.
Journal code: IFE. ISSN: 0022-1759.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199910
EW 19991003
AB To date, in vivo ***apoptosis*** within the thymus has been assessed
using morphological criteria and/or detection of a DNA ladder indicative
of oligonucleosomal fragmentation of the DNA. Here, we have used a
fluorometric method to investigate activation of the ***caspase***
protease family in the thymus following in vivo induction of
apoptosis by injection of the synthetic glucocorticoid
hydrocortisone. Cleavage of DEVD-MCA by ***caspase*** -3 and other
group II caspases releases free MCA which can be detected

fluorimetrically. We demonstrate a time-dependent increase in DEVD-MCA cleavage activity within this tissue indicating the activation of ***caspase*** -3 like enzymes. This activity was inhibited by the specific group II ***caspase*** inhibitor DEVD-CHO. The interpretation of increased ***caspase*** ***activity*** was confirmed by immunoblot analysis to reveal cleavage of the ***caspase*** -3 substrate, fodrin. In addition, agarose gel electrophoresis of the DNA yielded a ladder pattern, confirming the occurrence of ***apoptosis*** . This study demonstrates that DEVD-MCA cleavage activity may be a useful quantitative method for the analysis of ***apoptosis*** in thymus tissue. It is a relatively rapid procedure not requiring ***thymocyte*** isolation or gel electrophoresis and detects fairly early biochemical changes occurring during ***apoptosis*** . In the present study we have used this method to demonstrate the involvement of caspases in ***thymocyte*** apoptotic death induced in vivo by glucocorticoids. Thus, measurement of ***caspase*** ***activity*** in thymus tissue may have applications for studying the in vivo effects of immunotoxicants.

L8 ANSWER 2 OF 3 BIOSIS
COPYRIGHT 1999 BIOSIS
AN 1999:362609 BIOSIS
DN PREV199900362609
TI Application of a fluorometric ***assay*** to detect ***caspase*** ***activity*** in thymus tissue undergoing ***apoptosis*** in vivo.
AU Gorman, Adrienne M.; Hirt, Ulrich A.; Zhivotovsky, Boris; Orrenius, Sten; Ceccatelli, Sandra (1)
CS (1) Division of Toxicology, Institute of Environmental Medicine, Karolinska Institutet, S-171 77, Stockholm Sweden
SO Journal of Immunological Methods, (June 24, 1999) Vol. 226, No. 1-2, pp. 43-48.
ISSN: 0022-1759.
DT Article
LA English
SL English
AB To date, in vivo ***apoptosis*** within the thymus has been assessed using morphological criteria and/or detection of a DNA ladder indicative of oligonucleosomal fragmentation of the DNA. Here, we have used a fluorometric method to investigate activation of the ***caspase*** protease family in the thymus following in vivo induction of ***apoptosis*** by injection of the synthetic glucocorticoid hydrocortisone. Cleavage of DEVD-MCA by ***caspase*** -3 and other group II caspases releases free MCA which can be detected fluorimetrically. We demonstrate a time-dependent increase in DEVD-MCA

cleavage activity within this tissue indicating the activation of ***caspase*** -3 like enzymes. This activity was inhibited by the specific group II ***caspase*** inhibitor DEVD-CHO. The interpretation of increased ***caspase*** ***activity*** was confirmed by immunoblot analysis to reveal cleavage of the ***caspase*** -3 substrate, fodrin. In addition, agarose gel electrophoresis of the DNA yielded a ladder pattern, confirming the occurrence of ***apoptosis*** . This study demonstrates that DEVD-MCA cleavage activity may be a useful quantitative method for the analysis of ***apoptosis*** in thymus tissue. It is a relatively rapid procedure not requiring ***thymocyte*** isolation or gel electrophoresis and detects fairly early biochemical changes occurring during ***apoptosis*** . In the present study we have used this method to demonstrate the involvement of caspases in ***thymocyte*** apoptotic death induced in vivo by glucocorticoids. Thus, measurement of ***caspase*** ***activity*** in thymus tissue may have applications for studying the in vivo effects of immunotoxicants.

L8 ANSWER 3 OF 3 EMBASE
COPYRIGHT 1999 ELSEVIER SCI. B.V.

AN 1999252679 EMBASE
TI Application of a fluorometric ***assay*** to detect ***caspase*** ***activity*** in thymus tissue undergoing ***apoptosis*** in vivo.
AU Gorman A.M.; Hirt U.A.; Zhivotovsky B.; Orrenius S.; Ceccatelli S.
CS S. Ceccatelli, Institute of Environmental Medicine, Division of Toxicology, Karolinska Institutet, S-171 77 Stockholm, Sweden.

sandra.ceccatelli@imm.ki.se
SO Journal of Immunological Methods, (1999) 226/1-2 (43-48).
Refs: 21
ISSN: 0022-1759 CODEN: JIMMBG
PUI S 0022-1759(99)00054-X
CY Netherlands
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB To date, in vivo ***apoptosis*** within the thymus has been assessed using morphological criteria and/or detection of a DNA ladder indicative of oligonucleosomal fragmentation of the DNA. Here, we have used a fluorometric method to investigate activation of the ***caspase*** protease family in the thymus following in vivo induction of ***apoptosis*** by injection of the synthetic glucocorticoid hydrocortisone. Cleavage of DEVD-MCA by ***caspase*** -3 and other

group II caspases releases free MCA which can be detected fluorimetrically. We demonstrate a time-dependent increase in DEVD-MCA cleavage activity within this tissue indicating the activation of ***caspase*** -3 like enzymes. This activity was inhibited by the specific group II ***caspase*** ***activity*** was confirmed by immunoblot analysis to reveal cleavage of the ***caspase*** -3 substrate, fodrin. In addition, agarose gel electrophoresis of the DNA yielded a ladder pattern, confirming the occurrence of ***apoptosis*** . This study demonstrates that DEVD-MCA cleavage activity may be a useful quantitative method for the analysis of ***apoptosis*** in thymus tissue. It is a relatively rapid procedure not requiring ***thymocyte*** isolation or gel electrophoresis and detects fairly early biochemical changes occurring during ***apoptosis*** . In the present study we have used this method to demonstrate the involvement of caspases in ***thymocyte*** apoptotic death induced in vivo by glucocorticoids. Thus, measurement of ***caspase*** ***activity*** in thymus tissue may have applications for studying the in vivo effects of immunotoxicants.

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=> d his

     (FILE 'HOME' ENTERED AT
09:10:23 ON 22 OCT 1999)

     FILE 'MEDLINE, BIOSIS,
EMBASE, USPATFULL' ENTERED AT
09:11:46 ON 22 OCT
     1999
L1             8 S (IMMATURE
THYMOCYTE!) AND CASPASE
L2             4 DUP REM L1 (4
DUPLICATES REMOVED)
L3             4 S IDENTIF? AND
(ENHANC? CASPASE)
L4             2 DUP REM L3 (2
DUPLICATES REMOVED)
L5          3734 S THYMOCYTE?
AND (APOPTOSIS)
L6           285 S L5 AND
("ICE" OR CASPASE)
L7            80 S L6 AND ASSAY
L8             3 S L7 AND
(CASPASE ACTIVITY)

=> s l6 and l1
L9             8 L6 AND L1

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10            4 DUP REM L9 (4
DUPLICATES REMOVED)

=> s (identify agent!) and
(enhanc? caspase)
L11            0 (IDENTIFY
AGENT!) AND (ENHANC? CASPASE)

=> s agent! and (enhanc?
caspase)
L12            0 AGENT! AND
(ENHANC? CASPASE)

=> log off y
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=> s caspase and apoptosis

L1 2616 CASPASE AND APOPTOSIS

=> s assay caspase activity

L2 0 ASSAY CASPASE ACTIVITY

=> s l1 and (caspase activity)

L3 215 L1 AND (CASPASE ACTIVITY)

=> s (increase or enhance) and l3

L4 40 (INCREASE OR ENHANCE) AND L3

=> dup rem l4

PROCESSING COMPLETED FOR L4
L5 17 DUP REM L4 (23 DUPLICATES REMOVED)

=> d l5 1-17 bib ab

L5 ANSWER 1 OF 17 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1999010882 EMBASE
TI **Caspase** activation accompanying cytochrome c release from mitochondria is possibly involved in nitric oxide-induced neuronal **apoptosis** in SH-SY5Y cells.
AU Uehara T.; Kikuchi Y.; Nomura Y.
CS Dr. Y. Nomura, Department of Pharmacology, Graduate Sch. of Pharmaceut. Sci., Hokkaido University, Sapporo 060-0812, Japan
SO Journal of Neurochemistry, (1999) 72/1 (196-205).
Refs: 42
ISSN: 0022-3042 CODEN: JONRA
CY United States
DT Journal; Article
FS 008 Neurology and Neurosurgery
LA English
SL English
AB It is well known that caspases are produced as proforms, which are proteolytically cleaved and activated during **apoptosis** or programmed cell death. We report here that caspases are activated during **apoptosis** by treatment with NOC18, a nitric oxide (NO) donor. Our present experiments have examined the way in which NO induces neuronal cell death, using a new type of NO donor that spontaneously releases only NO without enzymatic metabolism. NOC18 induced **apoptosis** in human neuroblastoma SH-SY5Y cells in a concentration-and time-dependent manner as estimated by DNA fragmentation assay, FACScan analysis, and nuclear morphology. Oxyhemoglobin, an NO trapper, suppressed NOC18-triggered DNA fragmentation, indicating that NO from NOC18 is a real activator in this study. Upon the induction of **apoptosis**, an **increase** in **caspase**-3-like protease activity, but not

caspase- 1, was observed. Procaspase-2 protein, an inactive form of **caspase**-2, decreased dramatically. In addition, NOC18 also resulted in poly (ADP- ribose) polymerase (PARP) cleavage, yielding an 85-kDa fragment typical of **caspase activity**. Oxyhemoglobin blocked the decrease of procaspase-2 and the cleavage of PARP by NOC18 in a concentration-dependent manner. Moreover, NO elicited the release of cytochrome c into the cytosol during **apoptosis**. These results suggest that both stimulation of **caspase activity** and cytochrome c release are partly involved in NO-induced neuronal **apoptosis**.

L5 ANSWER 2 OF 17 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 98-520756 [44] WPIDS
DNC C98-156298
TI Identifying agents which inhibit or **enhance caspase activity** - and which may be used, e.g., in treatment of cancer or autoimmune diseases..
DC B04 D16
IN CLAYTON, L; OCAIN, T D; PATCH, R J; REINHERZ, E
PA (DAND) DANA FARBER CANCER INST INC; (PROC-N) PROCEPT INC
CYC 19
PI WO 9836057 A1 980820 (9844)* EN 62 pp
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA JP
ADT WO 9836057 A1 WO 98-US3524 980217
PRAI US 97-948124 971009; US 97-802474 970218
AB WO 9836057 A UPAB: 981210
A method for identifying an agent which inhibits a **caspase** expressed in immature thymocytes, comprising: (a) contacting the **caspase** (or an active derivative or fragment) with a **caspase** substrate in the presence of the agent; and (b) identifying inhibition of **caspase activity**.

Also claimed are: (1) identifying an agent which inhibits **caspase activity**, comprising: (a) contacting a thymocyte (or a cell lysate of this comprising a thymocyte capsase or procaspase) with the agent; and (b) identifying inhibition of **caspase activity**; (2) identifying an agent which enhances the **caspase** expressed in immature thymocytes, comprising: (a) contacting the **caspase** (or an active derivative or fragment) with a **caspase** substrate in the presence of the agent; and (b) identifying enhancement of **caspase activity**; (3) identifying an agent which enhances the **caspase** expressed in immature thymocytes, comprising: (a) contacting a thymocyte (or a cell lysate of this comprising the capsase or procaspase) with the agent; and (b) identifying enhancement of **caspase activity**; (4) inhibiting **apoptosis** in lymphocytes, comprising contacting the lymphocyte with an agent which inhibits a thymocyte **caspase**; (5) enhancing **apoptosis** in lymphocytes, comprising contacting the lymphocyte with an agent which enhances a thymocyte **caspase**; (6) treatment of autoimmune diseases in mammals, comprising administering an agent which enhances the activity of a thymocyte **caspase**; (7) enhancing immune responses against an antigen in mammals comprising administering: (i) an agent which inhibits the activity of a thymocyte **caspase** and; (ii) an antigen.

USE - Products identified by the above processes may be used in treatment of cancers (such as leukaemia or melanomas) and autoimmune diseases. Inhibition of **apoptosis** can result in inhibition of down-regulation of lymphocytes, resulting in a T cell receptor population with an increased proportion of autoreactive T cells, i.e., an increased occurrence of T cells which have specificity for the host animal's own cells (e.g. cancer cells). By the same token, increasing the activity of the **caspase** enzyme enhances **apoptosis** of self-recognising T cells, resulting in a decrease in the population of T

cells which are responsible for autoimmune disorders. The compounds may also be useful in treating infections, inflammatory diseases and neurodegenerative disorders.

ADVANTAGE- No further details.

Dwg.0/2

L5 ANSWER 3 OF 17 MEDLINE DUPLICATE 1
AN 1998187659 MEDLINE
DN 98187659
TI MEK kinase 1, a substrate for DEVD-directed caspases, is involved in genotoxin-induced **apoptosis**.
AU Widmann C; Gerwins P; Johnson N L; Jarpe M B; Johnson G L
CS Division of Basic Sciences, National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado 80206, USA.. johnsonlab@njc.org
NC CA58157 (NCI)
DK37871 (NIDDK)
DK48845 (NIDDK)
+
SO MOLECULAR AND CELLULAR BIOLOGY, (1998 Apr) 18 (4) 2416-29.
Journal code: NGY. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199807
AB MEK kinase 1 (MEKK1) is a 196-kDa protein that, in response to genotoxic agents, was found to undergo phosphorylation-dependent activation. The expression of kinase-inactive MEKK1 inhibited genotoxin-induced **apoptosis**. Following activation by genotoxins, MEKK1 was cleaved in a **caspase**-dependent manner into an active 91-kDa kinase fragment. Expression of MEKK1 stimulated DEVD-directed **caspase activity** and induced **apoptosis**. MEKK1 is itself a substrate for CPP32 (**caspase**-3). A mutant MEKK1 that is resistant to **caspase** cleavage was impaired in its ability to induce **apoptosis**. These findings demonstrate that MEKK1 contributes to the apoptotic response to genotoxins. The regulation of MEKK1 by genotoxins involves its activation, which may be part of survival pathways, followed by its cleavage, which generates a proapoptotic kinase fragment able to activate caspases. MEKK1 and caspases are predicted to be part of an amplification loop to **increase caspase activity** during **apoptosis**.

L5 ANSWER 4 OF 17 MEDLINE DUPLICATE 2
AN 1998292518 MEDLINE
DN 98292518
TI The regulation of reactive oxygen species production during programmed cell death.
AU Tan S; Sagara Y; Liu Y; Maher P; Schubert D
CS Cellular Neurobiology Laboratory, The Salk Institute for Biological Studies, La Jolla, California 92037, USA.
NC R01NS09658 (NINDS)
2F32NS10032 (NINDS)
1F32NS10279-2 (NINDS)
SO JOURNAL OF CELL BIOLOGY, (1998 Jun 15) 141 (6) 1423-32.
Journal code: HMV. ISSN: 0021-9525.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199809
EW 19980903

AB Reactive oxygen species (ROS) are thought to be involved in many forms of programmed cell death. The role of ROS in cell death caused by oxidative glutamate toxicity was studied in an immortalized mouse hippocampal cell line (HT22). The causal relationship between ROS production and glutathione (GSH) levels, gene expression, **caspase activity**, and cytosolic Ca2+ concentration was examined. An initial 5-10-fold **increase** in ROS after glutamate addition is temporally correlated with GSH depletion. This early **increase** is followed by an explosive burst of ROS production to 200-400-fold above control values. The source of this burst is the mitochondrial electron transport chain, while only 5-10% of the maximum ROS production is caused by GSH depletion. Macromolecular synthesis inhibitors as well as Ac-YVAD-cmk, an interleukin 1beta-converting enzyme protease inhibitor, block the late burst of ROS production and protect HT22 cells from glutamate toxicity when added early in the death program. Inhibition of intracellular Ca2+ cycling and the influx of extracellular Ca2+ also blocks maximum ROS production and protects the cells. The conclusion is that GSH depletion is not sufficient to cause the maximal mitochondrial ROS production, and that there is an early requirement for protease activation, changes in gene expression, and a late requirement for Ca2+ mobilization.

L5 ANSWER 5 OF 17 MEDLINE DUPLICATE 3
AN 1998362095 MEDLINE
DN 98362095
TI Delta9-tetrahydrocannabinol induces **apoptosis** in macrophages and lymphocytes: involvement of Bcl-2 and **caspase**-1.
AU Zhu W; Friedman H; Klein T W
CS Department of Medical Microbiology and Immunology, University of South Florida, College of Medicine, Tampa, Florida 33162, USA.
NC DA03646 (NIDA)
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1998 Aug) 286 (2) 1103-9.
Journal code: JP3. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199811
EW 19981101
AB **Apoptosis** is programed cell death characterized by certain cellular changes and regulated by various gene products including Bcl-2 and **caspase**-1. The marijuana cannabinoid, Delta9tetrahydrocannabinol (THC), has been reported to suppress in culture the proliferation of splenocytes and **increase** the release of IL-1 from macrophages; however, the mechanisms of these effects remain unclear. Because cannabinoids have also been reported to induce **apoptosis** and because the release of IL-1 and suppression of lymphoproliferation are related to **apoptosis**, we tested for the induction of **apoptosis** by THC in murine immune cell cultures. Splenocytes cultured with Con A for up to 24 hr showed evidence of DNA fragmentation determined by gel electrophoresis, terminal deoxynucleotide transferase-mediated dUTP-fluorescein nick end labeling and 3H-thymidine labeling and THC (15-30 microM) treatment increased fragmentation under these conditions. Resident peritoneal macrophages cultured with lipopolysaccharides showed no obvious fragmentation unless they were also treated with THC. Time course studies examining DNA fragmentation and cell membrane integrity (assessed by dye exclusion) showed that fragmentation preceded membrane damage indicating that THC induced **apoptosis** rather than cell necrosis. In addition, THC treatment of splenocytes resulted in a decrease of Bcl-2 mRNA and protein as measured by Northern

and Western blotting, respectively, and the drug induced **apoptosis** was blocked by the **caspase** inhibitor, Ac-Tyr-Val-Ala-L-aspartic acid aldehyde. These data suggest that THC treatment of cultured immune cells induces **apoptosis** through the regulation of Bcl-2 and **caspase activity**.

L5 ANSWER 6 OF 17 MEDLINE DUPLICATE 4
AN 1999032687 MEDLINE
DN 99032687
TI Role of superoxide in **apoptosis** induced by growth factor withdrawal.
AU Lieberthal W; Triaca V; Koh J S; Pagano P J; Levine J S
CS Renal Section, Department of Medicine, Boston University Medical Center, Boston, Massachusetts 02118, USA.
NC DK-37105 (NIDDK)
DK-52898 (NIDDK)
HL-53031 (NHLBI)
+
SO AMERICAN JOURNAL OF PHYSIOLOGY, (1998 Nov) 275 (5 Pt 2) F691-702.
Journal code: 3U8. ISSN: 0002-9513.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199902
EW 19990204
AB We have examined the role of reactive oxygen species (ROS) in **apoptosis** induced by growth factor deprivation in primary cultures of mouse proximal tubular (MPT) cells. When confluent monolayers of MPT cells are deprived of all growth factors, the cells die by **apoptosis** over a 10- and 14-day period. Both epidermal growth factor (EGF) and high-dose insulin directly inhibit **apoptosis** of MPT cells deprived of growth factors. Growth factor deprivation results in an **increase** in the cellular levels of superoxide anion while **apoptosis** of MPT cells induced by growth factor withdrawal is inhibited by a number of antioxidants and scavengers of ROS. Growth factor deprivation also results in activation of **caspase activity**, which is inhibited by EGF and high-dose insulin as well as by the ROS scavengers and antioxidants that inhibit **apoptosis**. The cell-permeant **caspase** inhibitor, z-Val-Ala-Asp-CH2F (zVAD-fmk), prevents the **increase** in **caspase activity** and markedly inhibits **apoptosis** induced by growth factor deprivation. However, zVAD-fmk had no effect on the increased levels of superoxide associated with growth factor deprivation. Thus we provide novel evidence that ROS play an important role in mediating **apoptosis** associated with growth factor deprivation. ROS appear to act upstream of caspases in the apoptotic pathway. We hypothesize that oxidant stress, induced by growth factor withdrawal, represents a signaling mechanism for the default pathway of **apoptosis**.

L5 ANSWER 7 OF 17 MEDLINE DUPLICATE 5
AN 1998285532 MEDLINE
DN 98285532
TI Inhibition of etoposide-induced **apoptosis** with peptide aldehyde inhibitors of proteasome.
AU Stefanelli C; Bonavita F; Stanic I; Pignatti C; Farruggia G; Masotti L; Guarnieri C; Caldarera C M
CS Department of Biochemistry 'G. Moruzzi', University of Bologna, Via Irnerio 48, I-40126 Bologna, Italy.. cstefan@biofarm.unibo.it
SO BIOCHEMICAL JOURNAL, (1998 Jun 15) 332 (Pt 3) 661-5.

Journal code: 9YO. ISSN: 0264-6021.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199809
EW 19980904
AB Recent investigations have indicated the involvement of proteasome in programmed cell death. The present studies show that although peptide aldehyde inhibitors of proteasome are by themselves weak inducers of **apoptosis**, they inhibit the apoptotic effect of the anticancer drug etoposide in rat thymocytes. Acetyl-Leu-Leu-norvalinal (LLnV-al) and other related peptide aldehydes inhibited the **increase** in **caspase activity** and DNA fragmentation that followed treatment with etoposide and their effect was related to their potency as proteasome inhibitors. To inhibit etoposide-induced **apoptosis**, LLnV-al must be present within 3 h of treatment with etoposide, in the same way as the inhibitor of protein synthesis cycloheximide must be. Etoposide caused a rapid accumulation of p53 protein that was not inhibited by LLnV-al, which was also a strong inducer of p53. Peptide aldehydes were also weak activators of **caspase activity** , suggesting that the same mechanism, i.e. the blocking of proteasome function, both triggers **apoptosis** and inhibits the effect of etoposide. These results are consistent with a model in which proteasome is selectively involved in the pathway used by etoposide to induce cell suicide.

L5 ANSWER 8 OF 17 MEDLINE DUPLICATE 6
AN 1998352825 MEDLINE
DN 98352825
TI MycN and IFNgamma cooperate in **apoptosis** of human neuroblastoma cells.
AU Lutz W; Fulda S; Jeremias I; Debatin K M; Schwab M
CS Department of Cytogenetics-0825, German Cancer Research Center, Heidelberg.
SO ONCOGENE, (1998 Jul 23) 17 (3) 339-46.
Journal code: ONC. ISSN: 0950-9232.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199810
EW 19981004
AB Neuroblastomas undergo spontaneous regression at an unusually high rate. The mechanisms are not clear, but **apoptosis** may be involved. A large proportion of neuroblastomas is characterized by amplification of MYCN. Using human neuroblastoma cells harbouring tetracycline controlled expression of MYCN we have analysed the role of the MycN protein and IFNgamma in cell death decision. Neither conditional expression of MYCN nor treatment with IFNgamma alone was sufficient to trigger cell death. However, when acting in concert MycN and IFNgamma efficiently triggered cell death, which was accompanied by DNA fragmentation and required **caspase activity**, two hallmarks of **apoptosis**.
MycN and IFNgamma may cooperate along at least two different pathways. First, IFNgamma increased the CD95 cell surface expression while MycN enhanced the cellular susceptibility for the CD95 mediated death signal. Second, IFNgamma treatment induced expression of BAK mRNA while MycN and IFNgamma in combination increased the amount of Bax protein, another activator of **apoptosis**, without a concomitant **increase** in BAX mRNA. MycN also increased cell death in response to TRAIL and TNFalpha, suggesting that enforced MYCN expression in general increases the susceptibility of neuroblastoma cells towards a variety of death stimuli.

L5 ANSWER 9 OF 17 MEDLINE DUPLICATE 7
AN 1998218565 MEDLINE
DN 98218565
TI Inhibition of **caspase activity** induces a switch from **apoptosis** to necrosis.
AU Lemaire C; Andreau K; Souvannavong V; Adam A
CS Institut de Biochimie, CNRS ERS 0571, Universite Paris-Sud, Orsay, France.. christophe.lemaire@bbmpc.u-psud.fr
SO FEBS LETTERS, (1998 Mar 27) 425 (2) 266-70.
Journal code: EUH. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199807
EW 19980705
AB The role of caspases in B lymphocyte cell death was investigated by using two broad spectrum inhibitors of the **caspase** family, Z-Asp-cmk and Z-VAD-fmk. They totally prevented spontaneous and drug-induced **apoptosis** and inhibited the CPP32/**caspase**-3-like activity exhibited by apoptotic cells. However, the suppression of **apoptosis** was not associated with a long-term **increase** of cell survival, but conversely, with a switch from apoptotic death to the necrotic form. These results strongly suggest that **apoptosis** and necrosis share common initiation pathways, the final issue being determined by the presence of an active **caspase**.

L5 ANSWER 10 OF 17 MEDLINE DUPLICATE 8
AN 1999065152 MEDLINE
DN 99065152
TI Hypoxia induces **apoptosis** in human neuroblastoma SK-N-MC cells by **caspase** activation accompanying cytochrome c release from mitochondria.
AU Araya R; Uehara T; Nomura Y
CS Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan.
SO FEBS LETTERS, (1998 Nov 13) 439 (1-2) 168-72.
Journal code: EUH. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199902
EW 19990204
AB We have attempted to elucidate the mechanism of apoptotic cell death induced by hypoxia (very low oxygen conditions) in neuronal cells. Human neuroblastoma SK-N-MC cells under hypoxic conditions resulted in **apoptosis** in a time-dependent manner estimated by DNA fragmentation assay and nuclear morphology stained with fluorescent chromatin dye. Pretreatment with Z-Asp-CH2-DCB, a **caspase** inhibitor, suppressed the DNA ladder in response to hypoxia in a concentration-dependent manner. An **increase** in **caspase** -3-like protease (DEVDase) activity was observed during **apoptosis** , but no **caspase**-1 activity (YVADase) was detected. To confirm the involvement of **caspase**-3 during **apoptosis**, Western blot analysis was performed using anti-**caspase**-3 antibody. The 20- and 17-kDa proteins, corresponding to the active products of **caspase**-3, were generated in hypoxia-challenged lysates in which processing of the full length form of **caspase**-3 was evident. With a time course similar to this **caspase**-3 activation, hypoxic stress caused the cleavage of PARP, yielding an 85-kDa fragment typical of

caspase activity. In addition, **caspase**-2 was also activated by hypoxia, and the stress elicited the release of cytochrome c into the cytosol during **apoptosis**. These results suggest that **caspase** activation and cytochrome c release play roles in hypoxia-induced neuronal **apoptosis**.

L5 ANSWER 11 OF 17 MEDLINE DUPLICATE 9
AN 1998259277 MEDLINE
DN 98259277
TI **Caspase** activation is an early event in anthracycline-induced **apoptosis** and allows detection of apoptotic cells before they are ingested by phagocytes.
AU Durrieu F; Belloc F; Lacoste L; Dumain P; Chabrol J; Dachary-Prigent J; Morjani H; Boisseau M R; Reiffers J; Bernard P; Lacombe F
CS Laboratoire d'Hematologie, Hopital Haut Leveque, Pessac, France.
SO EXPERIMENTAL CELL RESEARCH, (1998 May 1) 240 (2) 165-75.
Journal code: EPB. ISSN: 0014-4827.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199808
EW 19980802
AB An increasing number of methods are being described to detect apoptotic cells. However, attempts to detect apoptotic cells in clinical samples are rarely successful. A hypothesis is that apoptotic cells are cleared from the circulation by phagocytosis before they become detectable by conventional morphological or cytometric methods. Using LR73 adhering cells as phagocytes in a model of in vitro phagocytosis, we found that phagocytosis of daunorubicin (DNR)-treated U937, HL60, or K562 leukemia cell lines occurred prior to phosphatidylserine externalization, DNA hydrolysis, chromatin condensation, nuclear fragmentation, or mitochondrial potential alteration. Moreover DNR-treated K562 cells were eliminated by phagocytes while **apoptosis** was never observed by any of the above methods. By contrast, using a fluorometric batch analysis assay to detect **caspase activity** in ceramide- or DNR-treated cells (fluorogenic substrate for **caspase**), we found that **caspase activity** increased in **apoptosis** -committed cells before they were detected by flow cytometry or recognized by phagocytes. Similarly a **caspase activity** **increase** was detected in circulating mononuclear cells of luekemic patients 15 h after the beginning of anthracyclin treatment. We suggest that recent findings on enzymatic events (**caspase** activation) occurring in the early events of **apoptosis** must now allow the development of new markers for **apoptosis**, irrespective of the morphological features or internucleosomal fragmentation which are late events in **apoptosis**.

L5 ANSWER 12 OF 17 MEDLINE DUPLICATE 10
AN 1998192453 MEDLINE
DN 98192453
TI Chemosensitivity of solid tumor cells in vitro is related to activation of the CD95 system.
AU Fulda S; Los M; Friesen C; Debatin K M
CS Hematology/Oncology, University Children's Hospital, Ulm, Germany.
SO INTERNATIONAL JOURNAL OF CANCER, (1998 Mar 30) 76 (1) 105-14.
Journal code: GQU. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals; Cancer Journals
EM 199806
EW 19980603
AB We have identified the CD95 system as a key mediator of chemotherapy-induced **apoptosis** in leukemia and neuroblastoma cells. Here, we report that sensitivity of various solid tumor cell lines for drug-induced cell death corresponds to activation of the CD95 system. Upon drug treatment, strong induction of CD95 ligand (CD95-L) and **caspase activity** were found in chemosensitive tumor cells (Hodgkin, Ewing's sarcoma, colon carcinoma and small cell lung carcinoma) but not in tumor cells which responded poorly to drug treatment (breast carcinoma and renal cell carcinoma). Blockade of CD95 using F(ab')2 anti-CD95 antibody fragments markedly reduced drug-induced **apoptosis**, suggesting that drug-triggered **apoptosis** depended on CD95-L/receptor interaction. Moreover, drug treatment induced CD95 expression, thereby increasing sensitivity for CD95-induced **apoptosis**. Drug-induced **apoptosis** critically depended on activation of caspases (ICE/Ced-3-like proteases) since the broad-spectrum inhibitor of caspases zVAD-fmk strongly reduced drug-mediated **apoptosis**. The prototype substrate of caspases, poly(ADP-ribose) polymerase, was cleaved upon drug treatment, suggesting that CD95-L triggered autocrine/paracrine death via activation of caspases. Our data suggest that chemosensitivity of solid tumor cells depends on intact **apoptosis** pathways involving activation of the CD95 system and processing of caspases. Our findings may have important implications for new treatment approaches to **increase** sensitivity and to overcome resistance of solid tumors.

L5 ANSWER 13 OF 17 MEDLINE DUPLICATE 11
AN 1998322475 MEDLINE
DN 98322475
TI Thrombin is an extracellular signal that activates intracellular death protease pathways inducing **apoptosis** in model motor neurons.
AU Smirnova I V; Zhang S X; Citron B A; Arnold P M; Festoff B W
CS Neurobiology Research Laboratory (151R), Department of Veterans Affairs Medical Center, Kansas City, Missouri 64128, USA.
SO JOURNAL OF NEUROBIOLOGY, (1998 Jul) 36 (1) 64-80.
Journal code: JAM. ISSN: 0022-3034.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199812
EW 19981201
AB **Apoptosis**, often also termed "programmed cell death", occurs in normal development in the brain and spinal cord. Important to concepts of disease and potential intervention is the exciting finding that **apoptosis** is also found after neurotrauma and in a number of neurodegenerative diseases. Although the precise mechanism of neuronal cell loss remains unknown, much emphasis has been placed recently on the activation of cell death protease cascades within the cell. How these cascades may be activated, especially from extracellular influences, is currently poorly understood. Thrombin, the multifunctional coagulation protease, is an early phase modulator at sites of tissue injury and has been shown to induce cell death in neurons by an apoptotic mechanism by activating its receptor, PAR-1. Using a model motor neuronal cell line, NSC19, which we have shown undergoes **apoptosis** after treatment with classic **apoptosis** inducers such as the topoisomerase inhibitors camptothecin and etoposide, we unambiguously found that nanomolar thrombin induced characteristic signs of **apoptosis**.

unfreezable water and the nucleation temperature. The melt onset temperature correlated positively with the body water content. But no clear relationship was seen between the water content and the SCP, either because the springtails had low levels of cryoprotectants or because the **ice** nucleation **activity** was unaffected. However, long periods (7 months) at -2.5 degree C reduced the water content from 74 +- 10.1 to 43 +- 7.2% of fresh weight and lowered the SCP from -6.1 +- 2.1 to -15.5 +- 2.3 degree C. When given access to water these individuals regained their body weight within 24 h. During periods of desiccation water losses were attribute to the loss of freezable water with the unfreezable portion remaining almost constant at 16,5 +- 2.0%. It appears that O. arcticus may experience a reduction of body water during winter periods of sub-zero temperatures, which may lower its SCP and **enhance** its cold tolerance but that it can rapidly return to summer levels given access to free water during the spring melt.

L10 ANSWER 2 OF 5 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:502905 BIOSIS
DN PREV199699225261
TI Utility of microcosm studies for predicting phylloplane bacterium population sizes in the field.
AU Kinkel, L. L.; Wilson, M.; Lindow, S. E. (1)
CS (1) Dep. ESPM, Univ. California, 151 Hilgard Hall, Berkeley, CA 94720-3110
USA
SO Applied and Environmental Microbiology, (1996) Vol. 62, No. 9, pp. 3413-3423.
ISSN: 0099-2240.
DT Article
LA English
AB Population sizes of two **ice** nucleation-active strains of Pseudomonas syringae were compared on leaves in controlled environments and in the field to determine the ability of microcosm studies to predict plant habitat preferences in the field. The P. syringae strains investigated were the parental strains of recombinant deletion mutant strains deficient in **ice** nucleation **activity** that had been field tested for their ability to control plant frost injury. The population size of the P. syringae strains was measured after inoculation at three field locations on up to 40 of the same plant species that were studied in the growth chamber. There was seldom a significant relationship between the mean population size of a given P. syringae strain incubated under either wet or dry conditions in microcosms and the mean population size which could be recovered from the same species when inoculated in the field. Specifically, on some plant species, the population size recovered from leaves in the field was substantially greater than from that species in a controlled environment, while for other plant species field populations were significantly smaller than those observed under controlled conditions. Population sizes of inoculated P. syringae strains, however, were frequently highly positively correlated with the indigenous bacterial population size on the same plant species in the field, suggesting that the ability of a particular plant species to support introduced bacterial strains is correlated with its ability to support large bacterial populations or that indigenous bacteria **enhance** the survival of introduced strains. Microcosm studies therefore seem most effective at assessing possible differences between parental and recombinant strains under a given environmental regime but are limited in their ability to predict the specific population sizes or plant habitat preferences of bacteria on leaves under field conditions.

L10 ANSWER 3 OF 5 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1991:159840 BIOSIS
DN BA91:85640
TI ISOLATION OF **ICE** NUCLEATING ACTIVE BACTERIA FROM INSECTS.
AU LEE R E JR; STRONG-GUNDERSON J M; LEE M R; GROVE K S; RIGA T J
CS DEP. ZOOL., MIAMI UNIV., HAMILTON, OHIO 45011.
SO J EXP ZOOL, (1991) 257 (1), 124-127.
CODEN: JEZOAO. ISSN: 0022-104X.
FS BA; OLD
LA English
AB In preparation for winter many insects **enhance** the supercooling capacity of their body fluids by 25.degree.C or more, thereby avoiding the lethal effects of tissue freezing. A primary factor limiting supercooling capacity is the presence of nucleating agents the catalyze **ice** formation at high subzero temperatures. Two species of **ice** nucleating active (INA) bacteria, Enterobacter agglomerans and Enterobacter taylorae, the latter with previously unknown **ice** nucleating **activity**, were isolated from the gut of two species of field-collected beetles, Ceratoma trifurcata and Hippodamia convergens.
Ingestion of these INA bacteria greatly diminished the capacity of our insect model, H. convergens, to supercool and caused freezing at temperatures as high as 1.5.degree.C. Removal or masking of endogenous INA bacteria may be a major factor in the cold-hardening of freeze intolerant insects for winter survival. Furthermore, these bacteria may provide a novel biological insecticide to control overwintering pest insects by decreasing their natural capacity to supercool.

L10 ANSWER 4 OF 5 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1998268205 EMBASE
TI Differential activation of MAPK and **ICE/Ced**-3 protease in chemical- induced apoptosis: The role of oxidative stress in the regulation of mitogen- activated protein kinases (MAPKs) leading to gene expression and survival or activation of caspases leading to apoptosis.
AU Kong A.-N.T.; Yu R.; Lei W.; Mandlekar S.; Tan T.-H.; Ucker D.S.
CS A.-N.T. Kong, Pharmaceutics/Pharmacodynamics Dept., MC 865, Ctr. for Pharmaceut. Biotechnology, Chicago, IL, United States
SO Restorative Neurology and Neuroscience, (1998) 12/2-3 (63-70).
Refs: 86
ISSN: 0922-6028 CODEN: RNNEEL
CY Ireland
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
LA English
SL English
AB Chemical-induced oxidative stress to a cell can signal many cellular responses which include proliferation, differentiation, hemeostasis, apoptosis or necrosis. To better understand the underlying molecular mechanisms after exposure to chemicals, we investigated the signal transduction pathways, in particular the mitogen-activated protein kinase (MAPK) pathway and the **ICE/Ced**-3 protease (caspase) pathway, activated by different agents. Butylated hydroxyanisol (BHA) and its metabolite, t-butyl- hydroquinone (tBHQ), both are well known phenolic antioxidants used in food preservatives, strongly activated c-Jun N-terminal kinase 1 (JNK1) and/or extracellular signal-regulated protein kinase 2 (ERK2) in a dose- and time- dependent fashion. Pretreatment with free radical scavengers N-acetyl-L- cysteine (NAC), glutathione (GSH), or vitamin E, inhibited ERK2 activation and, to a much lesser extent, JNK1 activation by BHA and tBHQ, implicating the role of oxidative stress. Under conditions where JNK1 and ERK2 were activated, BHA also activated

transcription factors nuclear factor kappa B (NF-.kappa.B), activated-protein-1 (AP-1), and anti-oxidant response element (ARE), leading to induction of genes such as c-jun, and c-fos. At relatively high concentrations, BHA and tBHQ stimulated proteolytic **activity** of **ICE**/Ced3 cysteine proteases, and caused apoptosis, which was blocked by pretreatment with NAC. Further increase in concentrations lead to rapid cell death predominantly occurred via necrosis. Some naturally occurring phytochemicals, such as phenylethyl isothiocyanate (PEITC), green tea polyphenols (GTP), and sulfarophane, which have been shown to be potent inducers of Phase II enzymes, also differentially regulated the activities of JNK, ERK, or CPP- 32, in a time- and dose-dependent manner. Our data, together with the work of others, enable us to propose a model in which low concentrations of these chemicals (e.g., BHA, PEITC) activate MAPKs leading to induction of gene expression (e.g., c-jun, c-fos, GST) which may protect the cells against toxic insults and **enhance** cell survival. At relatively high concentrations, these agents activated both MAPKs, and the **ICE/Ced**-3 caspase pathway, leading to apoptosis. The exact mechanisms by which MAPK and caspases are activated by these agents are currently unknown, but may involve oxidative modification of glutathione (GSH) and/or protein thiols, and/or generation of secondary messengers, ceramide and calcium, which further activate downstream events. Taken together, our results suggest that chemicals including phenolic antioxidants activate MAPK pathways which may lead to the induction of genes producing protection and survival mechanisms, as well as the **ICE/Ced**-3 protease pathway, leading to apoptosis. The balancing amongst these pathways may dictate the fate of the cells upon exposure to chemicals.

L10 ANSWER 5 OF 5 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 96281939 EMBASE
TI Utility of microcosm studies for predicting phylloplane bacterium population sizes in the field.
AU Kinkel L.L.; Wilson M.; Lindow S.E.
CS Department of ESPM, 151 Hilgard Hall, University of California, Berkeley, CA 94720-3110, United States
SO Applied and Environmental Microbiology, (1996) 62/9 (3413-3423).
ISSN: 0099-2240 CODEN: AEMIDF
CY United States
DT Journal
FS 004 Microbiology
046 Environmental Health and Pollution Control
LA English
SL English
AB Population sizes of two **ice** nucleation-active strains of Pseudomonas syringae were compared on leaves in controlled environments and in the field to determine the ability of microcosm studies to predict plant habitat preferences in the field. The P. syringae strains investigated were the parental strains of recombinant deletion mutant strains deficient in **ice** nucleation **activity** that had been field tested for their ability to control plant frost injury. The population size of the P. syringae strains was measured after inoculation at three field locations on up to 40 of the same plant species that were studied in the growth chamber. There was seldom a significant relationship between the mean population size of a given P. syringae strain incubated under either wet or dry conditions in microcosms and the mean population size which could be recovered from the same species when inoculated in the

2/18/97 PR

field. Specifically, on some plant species, the population size recovered from leaves in the field was substantially greater than from that species in a controlled environment, while for other plant species field populations were significantly smaller than those observed under controlled conditions. Population sizes of inoculated P. syringae strains, however, were frequently highly positively correlated with the indigenous bacterial population size on the same plant species in the field, suggesting that the ability of a particular plant species to support introduced bacterial strains is correlated with its ability to support large bacterial populations or that indigenous bacteria **enhance** the survival of introduced strains. Microcosm studies therefore seem most effective at assessing possible differences between parental and recombinant strains under a given environmental regime but are limited in their ability to predict the specific population sizes or plant habitat

Strikingly, endonucleolysis was accompanied by an **increase** in **caspase**-3-like activity in cellular extracts, which correlated with both detection of **caspase**-induced signature cleavage of the cortical cytoskeleton component nonerythroid spectrin (alpha-fodrin) and identification of increased accessibility of a **caspase** cleavage domain, using an antibody (Ab127) made against a synthetic peptide KGDEVD.

Demonstrating that thrombin activation of death proteases was linked to cell death, we were able to inhibit thrombin-induced **apoptosis** by using a **caspase** family inhibitor, benzyloxycarbonyl-Asp-(oMe)-fluoromethyl ketone (Boc-D-FMK). These novel results demonstrate that thrombin serves as an extracellular "death signal" to activate intracellular protease pathways. These pathways lead to apoptotic cell death and can be modulated by inhibiting **caspase** **activity** downstream to PAR-1.

L5 ANSWER 14 OF 17 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1998399554 EMBASE
TI Role of superoxide in **apoptosis** induced by growth factor withdrawal.
AU Lieberthal W.; Triaca V.; Koh J.S.; Pagano P.J.; Levine J.S.
CS W. Lieberthal, Renal Section, Boston Medical Center, 88 East Newton St., Boston, MA 02118, United States
SO American Journal of Physiology - Renal Physiology, (1998) 275/5 44-5 (F691-F702).
Refs: 50
ISSN: 0363-6127 CODEN: AJPPFK
CY United States
DT Journal; Article
FS 002 Physiology
028 Urology and Nephrology
029 Clinical Biochemistry
LA English
SL English
AB We have examined the role of reactive oxygen species (ROS) in **apoptosis** induced by growth factor deprivation in primary cultures of mouse proximal tubular (MPT) cells. When confluent monolayers of MPT cells are deprived of all growth factors, the cells die by **apoptosis** over a 10- and 14-day period. Both epidermal growth factor (EGF) and high-dose insulin directly inhibit **apoptosis** of MPT cells deprived of growth factors. Growth factor deprivation results in an **increase** in the cellular levels of superoxide anion while **apoptosis** of MPT cells induced by growth factor withdrawal is inhibited by a number of antioxidants and scavengers of ROS. Growth factor deprivation also results in activation of **caspase** **activity**, which is inhibited by EGF and high-dose insulin as well as by the ROS scavengers and antioxidants that inhibit **apoptosis**. The cell-permeant **caspase** inhibitor, z-Val-Ala-Asp-CH2F (zVAD-fmk), prevents the **increase** in **caspase** **activity** and markedly inhibits **apoptosis** induced by growth factor deprivation. However, zVAD-fmk had no effect on the increased levels of superoxide associated with growth factor deprivation. Thus we provide novel evidence that ROS play an important role in mediating **apoptosis** associated with growth factor deprivation. ROS appear to act upstream of caspases in the apoptotic pathway. We hypothesize that oxidant stress, induced by growth factor withdrawal, represents a signaling mechanism for the default pathway of **apoptosis**.

L5 ANSWER 15 OF 17 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1998114758 EMBASE

TI Identification of gene family of caspases in rat kidney and altered expression in ischemia-reperfusion injury.
AU Kaushal G.P.; Singh A.B.; Shah S.V.
CS G.P. Kaushal, Univ. of Arkansas for Med. Sciences, 4301 W. Markham St., Little Rock, AR 72205, United States
SO American Journal of Physiology - Renal Physiology, (1998) 274/3 43-3 (F587-F595).
Refs: 65
ISSN: 0363-6127 CODEN: AJPPFK
CY United States
DT Journal; Article
FS 002 Physiology
LA English
SL English
AB In the present study, we demonstrate that rat kidney contains **caspase activity** that was markedly inhibited by specific peptide inhibitors of caspases but not by inhibitors of Ser, Cys, Asp, or metalloproteinases: Using primers based on the nucleotide sequence of known members of Ced- 3/interleukin-1.beta.-converting enzyme (ICE) family from human origin, we have identified by reverse-transcription (RT) polymerase chain reaction (PCR) analyses that rat kidney transcribes the genes for **caspase**-1: (ICE), **caspase**- 2 (Nedd2), **caspase**-3 (CPP32), and **caspase**-6 (Mch2). RT-PCR products, when subcloned and sequenced, provided full-length cDNAs for ICE (1,209 bp) and CPP32 (786 bp) and partial cDNA products for Mch2 (561 bp) and Nedd2 (811 bp). The sequence analysis of the **caspase** cDNAs showed conserved catalytic site QACRG as well as Asp cleavage site. Rat kidneys subjected to ischemia- reperfusion injury revealed differential expression of caspases with marked **increase** in CPP32 and ICE mRNA and proteins during reperfusion, transient **increase** in Nedd2 mRNA and proteins during ischemia and the early period of reperfusion, and little change in Mch2 expression during the ischemia or reperfusion period. The altered expression suggests that caspases may act in concert in a cascade and may play an important role in ischemic acute renal failure.

L5 ANSWER 16 OF 17 MEDLINE DUPLICATE 12
AN 1998025896 MEDLINE
DN 98025896
TI Cross-resistance of CD95- and drug-induced **apoptosis** as a consequence of deficient activation of caspases (ICE/Ced-3 proteases).
AU Los M; Herr I; Friesen C; Fulda S; Schulze-Osthoff K; Debatin K M
CS Hematology/Oncology, University Children's Hospital, Ulm, Germany.
SO BLOOD, (1997 Oct 15) 90 (8) 3118-29.
Journal code: A8G. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199801
AB The cytotoxic effect of anticancer drugs has been shown to involve induction of **apoptosis**. We report here that tumor cells resistant to CD95 (APO-1/Fas) -mediated **apoptosis** were cross-resistant to **apoptosis**-induced by anticancer drugs. **Apoptosis** induced in tumor cells by cytarabine, doxorubicin, and methotrexate required the activation of ICE/Ced-3 proteases (caspases), similarly to the CD95 system. After drug treatment, a strong **increase** of **caspase activity** was found that preceded cell death. Drug-induced activation of caspases was also found in ex vivo-derived T-cell leukemia cells. Resistance to cell death was

conferred by a peptide **caspase** inhibitor and CrmA, a poxvirus-derived serpin. The peptide inhibitor was effective even if added several hours after drug treatment, indicating a direct involvement of caspases in the execution and not in the trigger phase of drug action. Drug-induced **apoptosis** was also strongly inhibited by antisense approaches targeting **caspase**-1 and -3, indicating that several members of this protease family were involved. CD95-resistant cell lines that failed to activate caspases upon CD95 triggering were cross-resistant to drug-mediated **apoptosis**. Our data strongly support the concept that sensitivity for drug-induced cell death depends on intact **apoptosis** pathways leading to activation of caspases. The identification of defects in **caspase** activation may provide molecular targets to overcome drug resistance in tumor cells.

RB145 A2 B5 6

L5 ANSWER 17 OF 17 MEDLINE DUPLICATE 13
AN 97445203 MEDLINE
DN 97445203
TI Fluorometric and colorimetric detection of **caspase activity** associated with **apoptosis**.
AU Gurtu V; Kain S R; Zhang G
CS CLONTECH Laboratories, Inc., Palo Alto, California 94303, USA.
SO ANALYTICAL BIOCHEMISTRY, (1997 Aug 15) 251 (1) 98-102.
Journal code: 4NK. ISSN: 0003-2697.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
EW 19980104
AB The **caspase** (ICE/CED-3) family of proteases has been implicated to play a crucial role in **apoptosis**. However, the mechanisms by which **caspase activity** mediates **apoptosis** are not fully understood. Progress in this area has been limited due to the lack of a convenient and reliable system to quantify these protease activities. In this report, we describe a quantitative assay for the activity of **caspase**-3, a member of the **caspase** family thought to mediate **apoptosis** in most mammalian cell types. This assay utilizes a synthetic tetrapeptide, Asp-Glu-Val-Asp (DEVD), labeled with either a fluorescent molecule, 7-amino-4-trifluoromethyl coumarin (AFC), or a colorimetric molecule, p-nitroanilide (pNA) as substrates. DEVD-dependent protease activity is assessed by detection of the free AFC or pNA cleaved from the substrates. We demonstrate the utility of the assay for rapid quantification of **caspase**-3 activity in the onset of **apoptosis**. Using the assay, we show that **apoptosis** induced in 32D cells under various conditions is associated with an **increase** in the DEVD-dependent protease activity. These studies suggest that induction of the DEVD-dependent protease activity is an indicator of **apoptosis** and demonstrate the utility of the assays for assessment of the role of **caspase** -family proteases in apoptotic cell progression.

Parent has priority but Parent is wrongly Parent— No dependency!

QP501.A6

=> s agent! and l5

L6 3 AGENT! AND L5

=> d l6 1-3 ab bib

L6 ANSWER 1 OF 3 MEDLINE
AB Recent investigations have indicated the involvement of proteasome in programmed cell death. The present studies show that although peptide

aldehyde inhibitors of proteasome are by themselves weak inducers of **apoptosis**, they inhibit the apoptotic effect of the anticancer drug etoposide in rat thymocytes. Acetyl-Leu-Leu-norvalinal (LLnV-al) and other related peptide aldehydes inhibited the **increase** in **caspase activity** and DNA fragmentation that followed treatment with etoposide and their effect was related to their potency as proteasome inhibitors. To inhibit etoposide-induced **apoptosis**, LLnV-al must be present within 3 h of treatment with etoposide, in the same way as the inhibitor of protein synthesis cycloheximide must be. Etoposide caused a rapid accumulation of p53 protein that was not inhibited by LLnV-al, which was also a strong inducer of p53. Peptide aldehydes were also weak activators of **caspase activity**, suggesting that the same mechanism, i.e. the blocking of proteasome function, both triggers **apoptosis** and inhibits the effect of etoposide. These results are consistent with a model in which proteasome is selectively involved in the pathway used by etoposide to induce cell suicide.

AN 1998285532 MEDLINE
DN 98285532
TI Inhibition of etoposide-induced **apoptosis** with peptide aldehyde inhibitors of proteasome.
AU Stefanelli C; Bonavita F; Stanic I; Pignatti C; Farruggia G; Masotti L; Guarnieri C; Caldarera C M
CS Department of Biochemistry 'G. Moruzzi', University of Bologna, Via Irnerio 48, I-40126 Bologna, Italy.. cstefan@biofarm.unibo.it
SO BIOCHEMICAL JOURNAL, (1998 Jun 15) 332 (Pt 3) 661-5.
Journal code: 9YO. ISSN: 0264-6021.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199809
EW 19980904

L6 ANSWER 2 OF 3 MEDLINE
AB MEK kinase 1 (MEKK1) is a 196-kDa protein that, in response to genotoxic **agents**, was found to undergo phosphorylation-dependent activation. The expression of kinase-inactive MEKK1 inhibited genotoxin-induced **apoptosis**. Following activation by genotoxins, MEKK1 was cleaved in a **caspase**-dependent manner into an active 91-kDa kinase fragment. Expression of MEKK1 stimulated DEVD-directed **caspase activity** and induced **apoptosis**. MEKK1 is itself a substrate for CPP32 (**caspase**-3). A mutant MEKK1 that is resistant to **caspase** cleavage was impaired in its ability to induce **apoptosis**. These findings demonstrate that MEKK1 contributes to the apoptotic response to genotoxins. The regulation of MEKK1 by genotoxins involves its activation, which may be part of survival pathways, followed by its cleavage, which generates a proapoptotic kinase fragment able to activate caspases. MEKK1 and caspases are predicted to be part of an amplification loop to **increase caspase activity** during **apoptosis**.

AN 1998187659 MEDLINE
DN 98187659
TI MEK kinase 1, a substrate for DEVD-directed caspases, is involved in genotoxin-induced **apoptosis**.
AU Widmann C; Gerwins P; Johnson N L; Jarpe M B; Johnson G L
CS Division of Basic Sciences, National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado 80206, USA.. johnsonlab@njc.org
NC CA58157 (NCI)
DK37871 (NIDDK)
DK48845 (NIDDK)

SO MOLECULAR AND CELLULAR BIOLOGY, (1998 Apr) 18 (4) 2416-29.
Journal code: NGY. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199807

L6 ANSWER 3 OF 3 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AB WO 9836057 A UPAB: 981210
A method for identifying an agent which inhibits a **caspase** expressed in immature thymocytes, comprising: (a) contacting the **caspase** (or an active derivative or fragment) with a **caspase** substrate in the presence of the agent; and (b) identifying inhibition of **caspase activity**.

Also claimed are: (1) identifying an agent which inhibits **caspase activity**, comprising: (a) contacting a thymocyte (or a cell lysate of this comprising a thymocyte capsase or procaspase) with the agent; and (b) identifying inhibition of **caspase activity**; (2) identifying an agent which enhances the **caspase** expressed in immature thymocytes, comprising: (a) contacting the **caspase** (or an active derivative or fragment) with a **caspase** substrate in the presence of the agent; and (b) identifying enhancement of **caspase activity**; (3) identifying an agent which enhances the **caspase** expressed in immature thymocytes, comprising: (a) contacting a thymocyte (or a cell lysate of this comprising the capsase or procaspase) with the agent; and (b) identifying enhancement of **caspase activity**; (4) inhibiting **apoptosis** in lymphocytes, comprising contacting the lymphocyte with an agent which inhibits a thymocyte **caspase**; (5) enhancing **apoptosis** in lymphocytes, comprising contacting the lymphocyte with an agent which enhances a thymocyte **caspase**; (6) treatment of autoimmune diseases in mammals, comprising administering an agent which enhances the activity of a thymocyte **caspase**; (7) enhancing immune responses against an antigen in mammals comprising administering: (i) an agent which inhibits the activity of a thymocyte **caspase** and; (ii) an antigen.

USE - Products identified by the above processes may be used in treatment of cancers (such as leukaemia or melanomas) and autoimmune diseases. Inhibition of **apoptosis** can result in inhibition of down-regulation of lymphocytes, resulting in a T cell receptor population with an increased proportion of autoreactive T cells, i.e., an increased occurrence of T cells which have specificity for the host animal's own cells (e.g. cancer cells). By the same token, increasing the activity of the **caspase** enzyme enhances **apoptosis** of self-recognising T cells, resulting in a decrease in the population of T cells which are responsible for autoimmune disorders. The compounds may also be useful in treating infections, inflammatory diseases and neurodegenerative disorders.

ADVANTAGE- No further details.

Dwg.0/2
AN 98-520756 [44] WPIDS
DNC C98-156298
TI Identifying **agents** which inhibit or **enhance** **caspase activity** - and which may be used, e.g., in treatment of cancer or autoimmune diseases..
DC B04 D16
IN CLAYTON, L; OCAIN, T D; PATCH, R J; REINHERZ, E
PA (DAND) DANA FARBER CANCER INST INC; (PROC-N) PROCEPT INC
CYC 19
PI WO 9836057 A1 980820 (9844)* EN 62 pp
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE

W: CA JP
ADT WO 9836057 A1 WO 98-US3524 980217
PRAI US 97-948124 971009; US 97-802474 970218

=> s enhance and (yama or ICE or ced)

L7 349 ENHANCE AND (YAMA OR ICE OR CED)

=> s activity(3a)l7

PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'ACTIVITY(3A)L31'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'ACTIVITY(3A)L32'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'ACTIVITY(3A)L33'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'ACTIVITY(3A)L34'
L8 47 ACTIVITY(3A) L7

=> s activity(3a)(yama or ice or ced)

L9 821 ACTIVITY(3A)(YAMA OR ICE OR CED)

=> s l7 and l9

L10 5 L7 AND L9

=> d l10 1-5 bib ab

L10 ANSWER 1 OF 5 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:535772 BIOSIS
DN PREV199699258128
TI The relationship between water content and cold tolerance in the Arctic collembolan Onychiurus arcticus (Collembola: Onychiuridae.
AU Worland, Michael R.
CS British Antarctic Survey, Natural Environment Res. Council, High Cross, Madingley Road, Cambridge CB3 0ET UK
SO European Journal of Entomology, (1996) Vol. 93, No. 3, pp. 341-348. ISSN: 1210-5759.
DT Article
LA English
AB The Arctic collembolan Onychiurus arcticus is freezing intolerant and experiences temperatures below -25 degree C during winter periods of low air temperatures and only light snow cover. Summer collected individuals have a mean (+- SE) supercooling point of -6.1 +- 0.1 degree C. This study was designed to measure the desiccation resistance and subsequent recovery of O. arcticus from partial dehydration and relate these to its cold-hardiness in terms of changes in the supercooling point (SCP) and solute concentration. Drying curves measured with a recording microbalance showed two distinct phases characteristic of the loss of free and chemically bound (osmotically inactive) water. Rates of water loss at 0 degree C and low relative humidity (lt 5%) were similar to those measured for Antarctic Collembola (5% h-1 of the initial total water content). O. arcticus survived losses of 40% of its total body water content and recovered within 36 h but could not survive losses of 50% of its original water content. Differential scanning calorimetry was used to investigate the nature of the body water, i.e. the proportion of freezable to